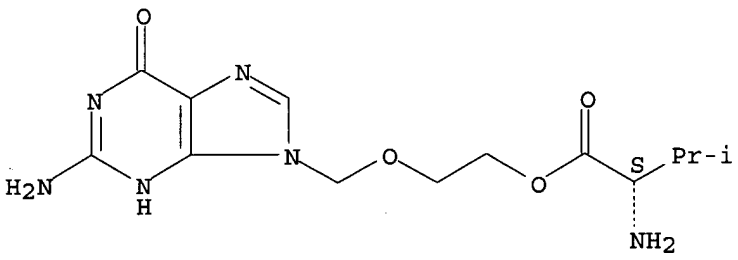
> d

L13 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **124832-27-5** REGISTRY
CN L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester, monohydrochloride (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 256U
CN 256U87 hydrochloride
CN BW 256
CN BW 256U87
CN Valaciclovir hydrochloride
CN Valacyclovir hydrochloride
CN Valtrex
FS STEREOSEARCH
DR 136489-37-7
MF C13 H20 N6 O4 . Cl H
SR CA
LC STN Files: ADISINSIGHT, ANABSTR, BIOSIS, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU, DRUGUPDATES, MEDLINE, MRCK*, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
CRN (124832-26-4)

Absolute stereochemistry.



● HCl

37 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
37 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>

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 s valacyclovir/cn
L8             1 VALACYCLOVIR/CN

=> d
                27-5
L8   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   124832-26-4  REGISTRY
CN   L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester
     (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   256U87
CN   L-Valine ester with 9-[(2-hydroxyethoxy)methyl]guanine
CN   Valaciclovir
CN   ValACV
CN   Valacyclovir
FS   STEREOSEARCH
MF   C13 H20 N6 O4
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CHEMCATS, CIN, DDFU, DIOGENES,
       DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT,
       SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO

Absolute stereochemistry.
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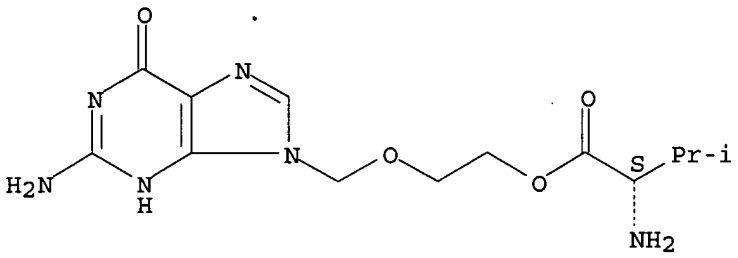


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             235 REFERENCES IN FILE CA (1957 TO DATE)
               7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             235 REFERENCES IN FILE CAPLUS (1957 TO DATE)


=>
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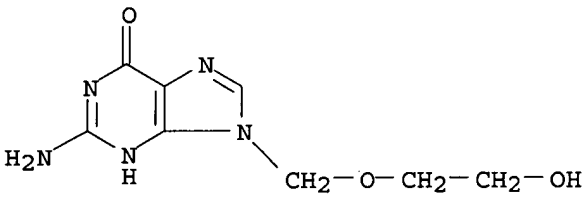
L7 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 59277-89-3 REGISTRY
CN 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 9-(2-Hydroxyethoxymethyl)guanine
CN Acicloftal
CN Aciclovir
CN ACV
CN Acyclo V
CN Acycloguanosine
CN **Acyclovir**
CN Avirase
CN BW 248U
CN Cargosil
CN Gerpevir
CN Herpevir
CN Poviral
CN Vipral
CN Virorax
CN Wellcome 248U
CN Zovirax
CN Zyclir
FS 3D CONCORD
MF C8 H11 N5 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



5/4/210

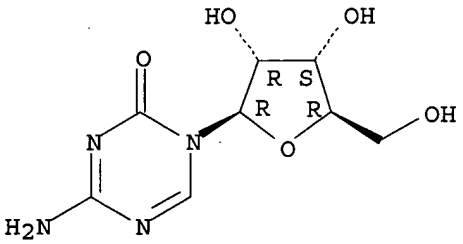
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2489 REFERENCES IN FILE CA (1957 TO DATE)
116 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2493 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 320-67-2 REGISTRY
CN 1,3,5-Triazin-2(1H)-one, 4-amino-1-.beta.-D-ribofuranosyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN s-Triazin-2(1H)-one, 4-amino-1-.beta.-D-ribofuranosyl- (8CI)
OTHER NAMES:
CN 5-AC
CN 5-AzaC
CN **5-Azacytidine**
CN 5-AZC
CN 5-AZCR
CN Antibiotic U 18496
CN Azacitidine
CN Azacytidine
CN Ladakamycin
CN Ledakamycin
CN Mylosar
CN NSC 102816
CN NSC 103-627
CN U 18496
CN WR 183027
FS STEREOSEARCH
DR 52934-49-3, 292869-98-8
MF C8 H12 N4 O5
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1254 REFERENCES IN FILE CA (1957 TO DATE)
22 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1258 REFERENCES IN FILE CAPLUS (1957 TO DATE)
19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L20 ANSWER 29 OF 30 WPIDS (C) 2003 THOMSON DERWENT
AN 1998-130427 [12] WPIDS
CR 2002-588740 [63]
DNC C1998-043071
TI Inducer of viral gene together with **antiviral** agent - for treating viral infections, including those associated with neoplasia and blood disorders, by pulsed administration of gene inducers.
DC B05 P14
IN FALLER, D V; PERRINE, S P; WHITE, B F
PA (FALL-I) FALLER D V; (PERR-I) PERRINE S P; (WHIT-I) WHITE B F; (UYBO-N) UNIV BOSTON
CYC 77
PI WO 9804290 A2 19980205 (199812)* EN 136p
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN YU
AU 9738891 A 19980220 (199828)
US 5939456 A 19990817 (199939)
EP 969869 A2 20000112 (200008) EN
R: BE CH DE FR GB GR IT LI
US 6197743 B1 20010306 (200115)
US 2001009922 A1 20010726 (200146)
JP 2001527517 W 20011225 (200204) 65p
ADT WO 9804290 A2 WO 1997-US12818 19970728; AU 9738891 A AU 1997-38891 19970728; US 5939456 A US 1996-687670 19960726; EP 969869 A2 EP 1997-936153 19970728, WO 1997-US12818 19970728; US 6197743 B1 US 1996-687671 19960726; US 2001009922 A1 Cont of US 1996-687671 19960726, US 2001-756489 20010108; JP 2001527517 W WO 1997-US12818 19970728, JP 1998-508931 19970728
FDT AU 9738891 A Based on WO 9804290; EP 969869 A2 Based on WO 9804290; US 2001009922 A1 Cont of US 6197743; JP 2001527517 W Based on WO 9804290
PRAI US 1996-687671 19960726; US 1996-687670 19960726; US 2001-756489 20010108
AB WO 9804290 A UPAB: 20021007
Inducer of viral gene and **antiviral** agent as a composition (A) which comprises (a) an agent (I) that induces expression of a viral product (II) in a virus-infected cell, and (b) an **antiviral** agent (III) directed against (II). Also claimed are: (1) the treatment of a cell proliferative disease by administration of an activator (IV), to activate expression of latent virus (episomal or integrated) and (III); (2) a composition containing di(m)ethyl butyrate (V); (3) treatment of human disorders by administration of numerous pulses of a non-toxic composition (A') with > 48 hour interval between pulses, or with an interval greater than the in vivo lifetime of (A'), and (4) a method for expanding a cell population by administering pulses of the composition of (3).

USE - (A) are used to kill virus-infected cells (especially those infected with a herpes, T or B cell leukaemia, adeno or hepatitis virus, especially Epstein-Barr virus, Kaposi-associated virus, human immune deficiency virus or human T cell lymphoma/leukaemia virus) and to treat virus-induced proliferative disease such as Burkitts lymphoma and leukaemia. The method of (3) is especially used to treat cell proliferative disease, cytopaenia (especially anaemia, leucopaenia or thrombocytopaenia) or haemoglobinopathy (especially **sickle cell** anaemia or thalassemia) (all claimed). The method of (4) is used to expand cells for subsequent return to a patient, e.g. for haematopoietic reconstitution.

(A) and (A') are administered orally, by injection, rectally or topically. A typical dose for arginine butyrate is 3-10 g/kg/month.

ADVANTAGE - Treatment with (I) makes infected cells more sensitive to (II), even when the infection is latent. The pulsed method of

administration reduces the dose required, to below 20% of that in continuous administration procedures, allowing use over long periods without significant side effects.
Dwg.4B/18

=>

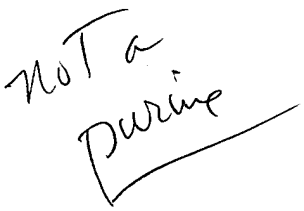
L32 ANSWER 320 OF 324 MEDLINE
AN 84265219 MEDLINE
DN 84265219 PubMed ID: 6205021
TI **Hydroxyurea** enhances fetal hemoglobin production in **sickle cell** anemia.
AU Platt O S; Orkin S H; Dover G; Beardsley G P; Miller B; Nathan D G
NC 1-KO400689 (NHLBI)
5P60 HL15157 (NHLBI)
5PO1 HL32262
+
SO JOURNAL OF CLINICAL INVESTIGATION, (1984 Aug) 74 (2) 652-6.
Journal code: 7802877. ISSN: 0021-9738.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198409
ED Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19840907
AB **Hydroxyurea**, a widely used cytotoxic/cytostatic agent that does not influence methylation of DNA bases, increases fetal hemoglobin production in anemic monkeys. To determine its effect in **sickle cell** anemia, we treated two patients with a total of four, 5-d courses (50 mg/kg per d, divided into three oral doses). With each course, fetal reticulocytes increased within 48-72 h, peaked in 7-11 d, and fell by 18-21 d. In patient I, fetal reticulocytes increased from 16.0 +/- 2.0% to peaks of 37.7 +/- 1.2, 40.0 +/- 2.0, and 32.0 +/- 1.4% in three successive courses. In patient II the increase was from 8.7 +/- 1.2 to 50.0 +/- 2.0%. Fetal hemoglobin increased from 7.9 to 12.3% in patient I and from 5.3 to 7.4% in patient II. Hemoglobin of patient I increased from 9.0 to 10.5 g/dl and in patient II from 6.7 to 9.9 g/dl. Additional single-day courses of **hydroxyurea** every 7-20 d maintained the fetal hemoglobin of patient I t 10.8-14.4%, and the total hemoglobin at 8.7-10.8 g/dl for an additional 60 d. The lowest absolute granulocyte count was 1,600/mm3; the lowest platelet count was 390,000/mm3. The amount of fetal hemoglobin per erythroid burst colony-forming unit (BFU-E)-derived colony cell was unchanged, but the number of cells per BFU-E-derived colony increased. Although examination of DNA synthesis in erythroid marrow cells in vitro revealed no decreased methylcytidine incorporation, Eco RI + Hpa II digestion of DNA revealed that hypomethylation of gamma-genes had taken place in vivo after treatment. This observation suggests that **hydroxyurea** is a potentially useful agent for the treatment of **sickle cell** anemia and that demethylation of the gamma-globin genes accompanies increased gamma-globin gene activity.

=>

L33 ANSWER 8 OF 12 MEDLINE
AN 83014912 MEDLINE
DN 83014912 PubMed ID: 6181507
TI 5-Azacytidine stimulates fetal hemoglobin synthesis in anemic baboons.
AU DeSimone J; Heller P; Hall L; Zwiers D
NC HL 20920-04 (NHLBI)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1982 Jul) 79 (14) 4428-31.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198212
ED Entered STN: 19900317
Last Updated on STN: 19970203
Entered Medline: 19821202
AB In an attempt to stimulate Hb F synthesis in baboons by means other than erythropoietic stress, we considered the possibility that an agent that inhibits methylation of CpG sequences in DNA may be effective. 5-Azacytidine, a cytosine analogue that cannot be methylated, is such an agent. Animals whose packed red cell volume was maintained at approximately 20% by bleeding were given 10 daily intravenous injections of the drug (6 mg/kg) in 12 days. Hb F levels in these animals started to increase on day 5 of this regimen and peak levels, which were 6-30 times higher than those produced by bleeding alone, occurred 5-7 days after the last dose of the drug. In animals previously identified as genetically "high" or "low" Hb F responders, the maximal Hb F levels were 70-85% and 35-40% respectively. In dose-response studies 5-azacytidine given daily at 3-4 mg/kg produced maximal Hb F increases. The drug did not correlate the percentage (number) of Hb F-containing cells (F cells) beyond the maximal number achieved by bleeding alone and thus its main effect was to increase Hb F per F cell. The finding that Hb F synthesis can be modulated to such a high degree by a drug may have therapeutic implications--e.g., in sickle cell anemia, in which stimulation of Hb F synthesis may **prevent sickling**.

not a purine

L10 ANSWER 8 OF 14 CA COPYRIGHT 2003 ACS
AN 102:125352 CA
TI 5-Azacytidine acts directly on both erythroid precursors and progenitors to increase production of fetal hemoglobin
AU Humphries, R. Keith; Dover, George; Young, Neal S.; Moore, Jeffrey G.; Charache, Samuel; Ley, Timothy; Nienhuis, Arthur W.
CS Clin. Hematol. Branch, Natl. Heart, Lung, Blood Inst., Bethesda, MD, 20205, USA
SO Journal of Clinical Investigation (1985), 75(2), 547-57
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB The effect of 5-azacytidine (I) [**320-67-2**] on erythroid precursors and progenitors was studied in patients with **sickle cell** anemia or severe thalassemia. Each patient received I i.v. for 5 or 7 days. I caused a 4-6-fold increase in .gamma.-globin in RNA concn. in bone marrow cells of 8 out of 9 patients and decreased the methylation frequency of a specific cytosine [71-30-7] residue in the .gamma.-globin gene promoter in all patients. Within 2 days of the start of I treatment there was a rise in the percentage of reticulocytes contg. fetal Hb [Hb F [9034-63-3]] without a significant change in the total no. of reticulocytes, which suggested that there was a direct action of I on erythroid precursors. Late erythroid progenitors (CFU-E), present in bone marrow after 2 days of drug administration, formed colonies contg. an increased amt. of Hb F as compared with control colonies. Moreover, the no. of CFU-E derived colonies was not decreased at these early times, which suggested that there was a direct action of I on erythroid progenitors in the absence of cytotoxicity. Exposure of normal bone marrow cells in tissue culture to I for 24 h reproduced both of these effects as judged during subsequent colony formation. The combined direct effects of I on both the erythroid precursor and progenitor compartments resulted in an increase in Hb F synthesis that was sustained for 2-3 wk. Toxicity to bone marrow as reflected by cytoredn. was evident after treatment in some patients but was not accompanied by an increase in Hb F prodn. A correlation was found between the effects of I on bone marrow, as assessed by in vitro measurements, and the hematol. response of the individual patients to I treatment.



L5 ANSWER 6 OF 9 MEDLINE
AN 2000052120 MEDLINE
DN 20052120 PubMed ID: 10586837
TI Acute renal insufficiency due to oral **acyclovir** in a man with **sickle cell** trait.
AU Lawson A F; Green P A; Brett A S
CS Department of Medicine, University of South Carolina School of Medicine, Columbia 29203, USA.
SO SOUTHERN MEDICAL JOURNAL, (1999 Nov) 92 (11) 1093-4.
Journal code: 0404522. ISSN: 0038-4348.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; AIDS
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991215
AB Several published reports have suggested that oral **acyclovir** can cause renal insufficiency, but baseline renal function was either abnormal or unclear in those reports. We describe a patient with oral **acyclovir**-induced acute renal failure and a normal serum creatinine level documented just before exposure to the drug. Conceivably, competition with a cephalosporin for renal tubular elimination predisposed our patient to nephrotoxic serum levels of **acyclovir**. In addition, the patient had **sickle cell** trait, which might have contributed to a disproportionate degree of hyperkalemia and acidosis seen early in the patient's clinical course.

L5 ANSWER 3 OF 9 MEDLINE
AN 2001284057 MEDLINE
DN 98703569 PubMed ID: 11367449
TI Hydroxyurea: what it is. New Mexico AIDS InfoNet.
AU Anonymous
SO Newsline People AIDS Coalit N Y, (1998 Mar) 15.
Journal code: 9603145.
CY United States
DT (NEWSPAPER ARTICLE)
LA English
FS AIDS
EM 199806
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19980623
AB Hydroxyurea (Hydrea) is an **antiviral** drug approved for use against cancer and **sickle cell** anemia. Produced by Bristol-Myers Squibb, it has not yet received Food and Drug Administration (FDA) approval for use against HIV; however, trial results are promising. The drug works by blocking a human cell enzyme used to multiply cells, and appears to be most effective when combined with reverse transcriptase inhibitors such as ddI or d4T. HIV does not develop resistance to hydroxyurea, and hydroxyurea can slow mutations in the virus. It is taken once or twice daily and is available in 500 mg tablets.

~~4, 7, 8~~, 10

~~93, 88~~ 183 81

148, 132, 127

L35 ANSWER 2 OF 2 MEDLINE
AN 2001029686 MEDLINE
DN 20529031 PubMed ID: 11074924
TI Successful treatment of hepatitis C in **sickle-cell** disease.
AU Swaim M W; Agarwal S; Rosse W F
SO ANNALS OF INTERNAL MEDICINE, (2000 Nov 7) 133 (9) 750-1. Journal code: 0372351. ISSN: 0003-4819.
CY United States
DT Letter
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001121

L32 ANSWER 302 OF 324 MEDLINE
AN 89333692 MEDLINE
DN 89333692 PubMed ID: 2757007
TI Effect of **hydroxyurea** on the rheological properties of sickle erythrocytes in vivo.
AU Ballas S K; Dover G J; Charache S
CS Cardeza Foundation for Hematologic Research, Philadelphia, PA 19107.
NC RR00035 (NCRR)
RR00722 (NCRR)
SO AMERICAN JOURNAL OF HEMATOLOGY, (1989 Oct) 32 (2) 104-11.
Journal code: 7610369. ISSN: 0361-8609.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198909
ED Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890907
AB We have monitored the rheological effects of **hydroxyurea** (HU) on erythrocytes obtained from two patients with severe **sickle cell** anemia who were enrolled in a therapeutic trial of this drug. Erythrocyte membrane stability and whole cell and membrane deformability of red cells from treated and untreated patients and normal controls were determined in room air using an ektacytometer--a laser viscodiffractometer. The percentage of dense cells was quantitated by centrifugation on a discontinuous Stractan density gradient. F reticulocytes (FR), absolute F reticulocytes (AFR), and F cells (FC) were determined by single-cell radial immunolgic assays. After 1 year of treatment with HU, there was a significant increase in the level of hemoglobin (Hb) F, FR, AFR, and FC. The degree of anemia remained the same, but there was significant increase in the mean cell volume (MCV) and a significant decrease in the mean corpuscular Hb concentration (MCHC). Whole cell deformability improved by twofold, but membrane stability remained within normal limits. The hydration status of sickle erythrocytes improved as was indicated by a change toward normal in gradient osmotic ektacytometry, an increase in RBC K+ content, a decrease in percent of dense cells, and a decrease in the MCHC. The data indicate that, in addition to its effect on the production of Hb, F, HU has a salutary effect on whole cell deformability and on the hydration status of sickle erythrocytes. Determination of the rheological properties of erythrocytes may be of value in monitoring the response to HU.

=>

L41 ANSWER 4 OF 6 MEDLINE
AN 90205983 MEDLINE
DN 90205983 PubMed ID: 1690857
TI Hematologic responses of patients with **sickle cell** disease to treatment with **hydroxyurea**.
AU Rodgers G P; Dover G J; Noguchi C T; Schechter A N; Nienhuis A W
CS Laboratory of Chemical Biology, NIDDK, National Institutes of Health, Bethesda, MD 20892.
NC HL-28028 (NHLBI)
SO NEW ENGLAND JOURNAL OF MEDICINE, **(1990 Apr 12)** 322 (15) 1037-45. Journal code: 0255562. ISSN: 0028-4793.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199004
ED Entered STN: 19900601
Last Updated on STN: 19960129
Entered Medline: 19900427
AB Because fetal hemoglobin contains gammaglobin chains instead of beta chains, it is not affected by the genetic defect that causes **sickle cell** disease. Increased levels of fetal hemoglobin decrease the tendency toward intracellular polymerization of sickle hemoglobin that characterizes this disease. **Hydroxyurea** is one of several cytostatic agents that have been shown to increase the production of fetal hemoglobin in some patients with **sickle cell** disease. We studied the effects of **hydroxyurea** administration in 10 hospitalized patients with **sickle cell** disease, each of whom was treated for three months. Seven patients responded with a 2- to 10-fold increase in fetal hemoglobin, from a mean (+/- SD) of 1.6 +/- 1.6 percent of total hemoglobin to 6.8 +/- 4.7 percent; three patients had fetal-hemoglobin levels of 10 to 15 percent of total hemoglobin. Three did not respond to treatment. Four of the patients who responded were retreated with **hydroxyurea** after one to four months without treatment and were found to have larger increases in fetal-hemoglobin levels. In most patients, levels were still rising at the end of the study, even after 90 days of therapy. Fetal-hemoglobin levels tended to peak at dosages of **hydroxyurea** that were myelosuppressive. In the patients who responded to treatment, there were significant increases in the percentage of reticulocytes and erythrocytes containing fetal hemoglobin and in the amount of fetal hemoglobin within these cells. The percentage of dense red cells decreased in the patients who responded to treatment. The tendency toward intracellular polymerization at physiologic oxygen saturation was reduced by about 33 percent in the cells containing fetal hemoglobin, whereas there was no change in the other cells. We conclude that **hydroxyurea** is effective in increasing the production of fetal hemoglobin, which in this study was found to be associated with a small decrease in hemolysis and an increase in hemoglobin levels despite myelosuppression. Controlled, prospective trials are necessary to establish whether these effects will lead to clinical benefit.

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=> d pn 176 156 150 87 56 l28

L28  ANSWER 176 OF 198  USPATFULL
PI     US 5939456              19990817

L28  ANSWER 156 OF 198  USPATFULL
PI     US 6197743         B1   20010306

L28  ANSWER 150 OF 198  USPATFULL
PI     US 2001009922      A1   20010726

L28  ANSWER 87 OF 198  USPATFULL
PI     US 2002120098      A1   20020829

L28  ANSWER 56 OF 198  USPATFULL
PI     US 2002188011      A1   20021212


=> d his
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L32 ANSWER 148 OF 324 MEDLINE
AN 1999186503 MEDLINE
DN 99186503 PubMed ID: 10088642
TI Long-term **hydroxyurea** treatment in young **sickle cell** patients.
AU Maier-Redelsperger M; Labie D; Elion J
CS Service d'Hematologie Biologique et INSERM U 458, hopital Tenon, Paris, France.
SO CURRENT OPINION IN HEMATOLOGY, (1999 Mar) 6 (2) 115-20. Ref: 50
Journal code: 9430802. ISSN: 1065-6251.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990525
AB **Hydroxyurea** is the first drug that, under well-organized, large-scale trials in adults, has shown a beneficial effect on the clinical course of **sickle cell** disease. Several small-scale trials have been conducted in children, but they used different therapeutic schedules, and only one was a single-blind crossover trial. Still, children are clearly good responders to the treatment because a rapid clinical improvement was observed, with decreased frequencies of vaso-occlusive crises, acute chest syndromes, and transfusion requirements. Despite large interindividual variations, virtually all the children studied increased their fetal hemoglobin, mean corpuscular volume, and total hemoglobin. Follow-up varied from 6 months to 59 months. More than in adults, the fetal hemoglobin increase was sustained, and few side effects were observed. Large-scale, placebo-controlled studies seem no longer needed. Guidelines concerning patient selection, dosing schedules, and monitoring protocols as well as exhaustive registries for the detection of long-term side effects are necessary.

L32 ANSWER 93 OF 324 MEDLINE
AN 2001203447 MEDLINE
DN 21111214 PubMed ID: 11172667
TI **Sickle cell** anemia and antisickling agents then and now.
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SO CURRENT MEDICINAL CHEMISTRY, (2001 Feb) 8 (2) 79-88. Ref: 171
Journal code: 9440157. ISSN: 0929-8673.
CY Netherlands
DT Historical
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200104
ED Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412
AB **Sickle cell** anemia is a genetic blood disorder arising from a point mutation in the beta-globin gene that leads to the replacement of glutamic acid residue by valine at the sixth position of the beta--chain of hemoglobin. At low oxygen tension, the mutant hemoglobin, sickle hemoglobin, polymerizes inside the red blood cells into a gel or further into fibers leading to a drastic decrease in the red cell deformability. As a result, micro-vascular occlusion arises which may lead to serious, sometimes fatal, crises. The present article reviews the historical, genetic, molecular, cellular, and clinical aspects of the disease. A review for the development and design of drugs to treat **sickle cell** anemia is presented. Anti-sickling agents are classified, based on the target to be modified, into three classes: the gene, the sickle hemoglobin molecule, and the red cell membrane modifiers. In spite of the full understanding of the pathology, physiology, and the molecular nature of the disease, and the development of large number of antisickling agents, a cure for **sickle cell** anemia still is unavailable. Strategies to treat **sickle cell** anemia since the early times of the disease state discovery in 1910, has focussed mainly on prophylactic measures to alleviate the painful crises. The article addresses clinical approaches used then and now to treat the disease, and the rationale of their use. Currently in clinical practice, **hydroxyurea** is the most commonly used agent to treat the disease, and it has been recently approved by the united states Food and Drug Administration as a drug for that purpose.

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